



Editorial

Hypersensitivity Pneumonitis. Toward a Less Invasive Diagnostic Procedure[☆]



Neumonitis por hipersensibilidad. Estudio diagnóstico menos invasivo

 Ferran Morell,^{a,b,c,*} Iñigo Ojanguren,^{a,b,c} María Jesús Cruz^{a,c}
^a Vall d'Hebron Institut de Recerca (VHIR), Servei de Pneumologia, Hospital Universitari Vall d'Hebron, Barcelona, Spain

^b Departament de Medicina, Universitat Autònoma de Barcelona, Barcelona, Spain

^c CIBER Enfermedades Respiratorias CIBERES, Barcelona, Spain

Pulmonologists treating patients with interstitial lung disease (ILD) know that there is some chance that the diagnosis will be hypersensitivity pneumonitis (HP). To arrive at that diagnosis, we must remember that HP patients are usually non-smokers, younger than 60 years of age, almost always without nail clubbing, normal auscultation, or else auscultation with non-velcro crackles, and occasionally, a few high-pitched, end-inspiratory wheezes, known as chirping rales.^{1,2}

In the acute form, high-resolution computed tomography (HRCT) will reveal the characteristic centrilobular nodules and ground glass opacities, particularly in the upper lobes and in the middle lobe and lingula, or a mosaic attenuation pattern with ground glass opacities combined with other clear/hyperlucent areas indicating hyperinflation from inflammatory centrilobular bronchiolar involvement. In the chronic form, mosaic attenuation patterns and centrilobular nodules, already indicating some degree of fibrosis, will be visualized, along with honeycombing areas, also in the lung bases. HP cannot be ruled out if HRCT shows images of usual interstitial pneumonia, non-specific interstitial pneumonia, or organizing pneumonia, and even if a combination of emphysema and fibrosis is revealed.

A meticulous case history must be obtained, looking for evidence of previous contact with birds, feathers (down comforters, etc.), or fungi (damp environments, aerosols with contaminated water, spas, steam iron, moldy walls, etc.). Other etiologies, such as isocyanates, cutting fluids, inhaled proteins, hard metals, etc., are less common. Specific immunoglobulin G (sIgG) against the serum (but not the droppings) of various birds and some fungi will be determined. This will help clarify if there has been contact with these antigens, inducing an immunological response.

Bronchoalveolar lavage (BAL) and cryobiopsy should be performed, since a lymphocyte concentration of greater than 20% in

BAL and in the biopsy, interstitial lymphoplasmacytic inflammation, along with bronchiolitis, and in some cases the finding of granulomas or giant cells in the interstitium will help confirm the diagnosis. Transbronchial biopsy in ILD has a low diagnostic yield of around 20%–38%.^{3,4}

If the cause is suspected to be an organic material or liquid possibly contaminated by fungi, a culture should be performed to identify the microorganisms.

Finally, if the patient interview and/or positive sIgG results and/or culture raises the suspicion of an antigen, a specific bronchial challenge test using that antigen is recommended. If positive, this procedure will even help suggest an etiological diagnosis. This diagnostic accuracy is important, since avoiding exposure to the specific cause will improve the course of the disease.

Surgical lung biopsy (SLB) should only be performed in those few cases in which a diagnosis cannot be reached after conducting the above-mentioned clinical tests.^{1,2}

Although this diagnostic protocol has been followed in some expert centers since 1976,⁵ it is striking to see that many centers with widely published experience in the study of ILD according to the recommendations of the international guidelines only obtain clinical history, physical examination, and HCRT. In European hospitals, sIgG detection and BAL are usually performed, and cryobiopsy is currently performed before deciding whether to perform SLB; in contrast, many experts in North America indicate SLB directly, as this is considered the gold standard for the diagnosis of HP.

The question lies in the diagnostic reliability of each of the tests. Quantitative methods such as ELISA have high sensitivity and low specificity for the detection of sIgG antibodies; moreover, the reliability of these techniques has only been studied for some of the antigens that induce HP. The sensitivity of qualitative methods, such as precipitin detection, is low. Determination of sIgG using quantitative methods is of great interest to experienced centers, since a positive result will: (1) establish an association between exposure and disease; (2) in the absence of suspicion on case history, positivity will hint at the possible cause; and (3) conversely, negativity, if that is the case, will determine that the HP is not secondary to exposure to fungi or feathers.

[☆] Please cite this article as: Morell F, Ojanguren I, Cruz MJ. Neumonitis por hipersensibilidad. Estudio diagnóstico menos invasivo. Arch Bronconeumol. 2018;54:445–446.

* Corresponding author.

E-mail address: fmorell@vhebron.net (F. Morell).

Doubts about the effectiveness of BAL can be largely dispelled by findings of recent publications that show that a percentage of lymphocytes higher than 30%,⁶ or even higher than 20%,⁷ is very suggestive of HP. Similarly, the diagnostic yield of cryobiopsy in ILD, when compared with that of SLB, appears to have been sufficiently proven.^{8,9}

In many studies, the specific bronchial challenge test has already demonstrated its diagnostic effectiveness in some types of HP caused by the more common antigens.¹⁰

In our opinion, the most appropriate clinical and ethical approach is to continue using the diagnostic protocol that we have recommended, because until validation studies are conducted on all these diagnostic procedures, many patients will be subjected unnecessarily to an SLB, with all the discomfort and complications that this entails.¹¹ Very recent recommendations from other experts in HP are in line with our proposal.¹²

References

1. Morell F, Villar A, Ojanguren I, Muñoz X, Cruz MJ. Hypersensitivity pneumonitis: challenges in diagnosis and management. Avoiding surgical lung biopsy. *Semir Respir Care Med.* 2016;37:395–405.
2. Morell F, Villar A. Fibrosis pulmonar (idiopática): estudio diagnóstico con 10 actuaciones clínicas. *Med Clin (Barc).* 2017;149:253–5.
3. Sheth JS, Belperio JA, Fishbein MC, Karezooni EA, Langstein A, Murray S, et al. Utility of transbronchial vs surgical lung biopsy in the diagnosis of suspected fibrotic interstitial lung disease. *Chest.* 2017;151:389–99.
4. Morell F, Reyes L, Doménech G, de Gracia J, Majó J, Ferrer J. Diagnoses and lung diagnostic procedures in 500 consecutive patients with clinical suspicion of interstitial lung disease. *Arch Bronconeumol.* 2008;44:185–91.
5. Tornos MP, Guardia J, Fuentes F, Gallart MT, Roca A, Morera J, et al. Pulmón del cuidador de aves. Experiencia en 4 casos. *Med Clin.* 1976;67:6–9.
6. Ohshimo S, Bonella F, Cui A, Beume M, Kohno N, Guzman J, et al. Significance of bronchoalveolar lavage for the diagnosis of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med.* 2009;179:1043–7.
7. Morell F, Villar A, Montero MA, Muñoz X, Colby TV, Pipvath S, et al. Chronic hypersensitivity pneumonitis in patients diagnosed with idiopathic pulmonary fibrosis: a prospective case-cohort study. *Lancet Respir Med.* 2013;1:685–94.
8. Sharp C, McCabe M, Adamali H, Medford AR. Use of transbronchial cryobiopsy in the diagnosis of interstitial lung disease—a systematic review and cost analysis. *QJM.* 2017;110:207–14.
9. Iftikhar IH, Alghothani L, Sardi A, Berkowitz D, Musani AI. Transbronchial lung cryobiopsy and video-assisted thoracoscopic lung biopsy in the diagnosis of diffuse parenchymal lung disease: a meta-analysis of diagnostic test accuracy. *Ann Am Thorac Soc.* 2017;14:1197–211.
10. Muñoz X, Sánchez-Ortiz M, Torres F, Villar A, Morell F, Cruz MJ. Diagnostic yield of specific inhalation challenge in hypersensitivity pneumonitis. *Eur Respir J.* 2014;44:1658–65.
11. Han Q, Luo Q, Xie JX, Wu LL, Liao LY, Zhang XX, et al. Diagnostic yield and postoperative mortality associated with surgical lung biopsy for evaluation of interstitial lung diseases: a systematic review and meta-analysis. *J Thorac Cardiovasc Surg.* 2015;149:1394–401.
12. Vasakova M, Morell F, Walsh S, Leslie K, Raghu G. Hypersensitivity pneumonitis: perspectives in diagnosis and management. *Am J Respir Crit Care Med.* 2017;196:680–9.